The Impact of a Concurrent Exercise Program With Metformin and Rosiglitazone on Glycemic Control

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The Impact of a Concurrent Exercise Program With Metformin and Rosiglitazone on Glycemic Control

Abstract

Background: Type 2 diabetes mellitus is a growing disorder throughout the world. Two of the major treatment modalities are used concurrently to fight inadequate glycemic control is exercise and diabetic medications. Metformin and rosiglitazone are diabetic medications known to improve glycemic control. Metformin lowers exercise capacity in diabetics while rosiglitazone improves exercise capacity. Given the impact of metformin and rosiglitazone on exercise capacity, the overall improvements in glycemic control, when used with a concurrent exercise program, needs to be examined.

Method: An exhaustive search of available medical literature was conducted using Medline-OVID, EBSCO-CINAHL and Web of Science using the keywords: type 2 diabetes mellitus, metformin, rosiglitazone, insulin resistance and exercise. Relevant articles were assessed for quality using GRADE.

Results: The search resulted in two studies that met inclusion criteria to be in this systematic review. The first study was a controlled trial with 32 participants and demonstrated that metformin does not accentuate the insulin sensitivity of exercise alone. The second study was a randomized controlled trial with 100 participants and demonstrated that rosiglitazone plus exercise improved glycemic control more than either treatment alone.

Conclusion: Although the amount and quality of evidence on the subject is lacking, these results have implications for clinical practice when individualizing patient treatment plans. Metformin and exercise do not have additive effects on glycemic control while rosiglitazone and exercise complement each other and do provide additive effects over time on glycemic control. Further research is needed to expand on the interactions between exercise and these diabetic medications on glycemic control, HbA1c and fasting glucose levels.

Keywords: Type 2 diabetes mellitus, metformin, rosiglitazone, exercise, insulin resistance and glycemic control.

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Keywords
Type 2 diabetes mellitus, metformin, rosiglitazone, exercise, insulin resistance and glycemic control

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The Impact of a Concurrent Exercise Program With Metformin and Rosiglitazone on Glycemic Control

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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Biography

[Redacted for privacy]
Abstract

**Background:** Type 2 diabetes mellitus is a growing disorder throughout the world. Two of the major treatment modalities are used concurrently to fight inadequate glycemic control is exercise and diabetic medications. Metformin and rosiglitazone are diabetic medications known to improve glycemic control. Metformin lowers exercise capacity in diabetics while rosiglitazone improves exercise capacity. Given the impact of metformin and rosiglitazone on exercise capacity, the overall improvements in glycemic control, when used with a concurrent exercise program, needs to be examined.

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**Results:** The search resulted in two studies that met inclusion criteria to be in this systematic review. The first study was a controlled trial with 32 participants and demonstrated that metformin does not accentuate the insulin sensitivity of exercise alone. The second study was a randomized controlled trial with 100 participants and demonstrated that rosiglitazone plus exercise improved glycemic control more than either treatment alone.

**Conclusion:** Although the amount and quality of evidence on the subject is lacking, these results have implications for clinical practice when individualizing patient treatment plans. Metformin and exercise do not have additive effects on glycemic control while rosiglitazone and exercise complement each other and do provide additive effects over time on glycemic control. Further research is needed to expand on the interactions between exercise and these diabetic medications on glycemic control, HbA1c and fasting glucose levels.

**Keywords:** Type 2 diabetes mellitus, metformin, rosiglitazone, exercise, insulin resistance and glycemic control.
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Table I: Characteristics of Reviewed Studies

List of Abbreviations

T2DM .......................................................... Type 2 Diabetes Mellitus
HbA1c .......................................................... Hemoglobin A1C
The Impact of a Concurrent Exercise Program With Metformin and Rosiglitazone on Glycemic Control

BACKGROUND

Insulin resistance and impaired insulin secretion leads to the hyperglycemic state that develops into type 2 diabetes mellitus (T2DM). Treatment regimens include both exercise and diabetic medications to help control glucose levels and improve insulin sensitivity. As little as one week of vigorous exercise can improve peripheral insulin sensitivity and suppress hepatic glucose production. Therefore, it is important to include exercise as a treatment option for those with and those at risk of developing T2DM. Metformin and rosiglitazone are common diabetes medications. Metformin has been found to improve glycemic control, decrease cardiovascular disease risk factors and decrease insulin resistance. Similarly, rosiglitazone has been found, in patients with T2DM, to improve insulin responsiveness. Because these therapeutic drugs are prescribed simultaneously with exercise, it is important to understand how these drugs might affect the patient's ability to exercise.

Previous studies have looked at how metformin and rosiglitazone may increase or decrease a patient's ability to exercise. In one study, metformin was found to increase patient's heart rate at submaximal exercise and increase perceived exertion, leading to a decrease in patients selected exercise intensity. Another study showed that peak heart rate was reduced significantly along with peak ventilation, peak oxygen uptake, peak respiratory exchange rate and exercise duration while taking metformin. If a patient taking metformin has an increased heart rate doing submaximal exercise but a decreased heart rate doing maximal exercise, their overall ability to exercise will be decreased.
Conversely, rosiglitazone has been found to actually increase maximal oxygen consumption and improve exercise capacity in patients with T2DM. One study shows that diabetic patients have a decrease in blood flow and endurance during isometric exercise that could be partially reversed with treatment using rosiglitazone for three months. Therefore it seems that metformin limits exercise capabilities while rosiglitazone can improve them in diabetic patients. It is important to understand how exercise affects the results of metformin and rosiglitazone because exercise is prescribed concurrently with diabetic medications in the hope of additive affects on glycemic control. The purpose of this systematic review is to determine if a concurrent, supervised exercise regimen with metformin or rosiglitazone affects the drug's ability to improve insulin resistance in patients with or at risk of developing T2DM.

METHODS

An exhaustive literature search using the search engines Medline-OVID, EBSCO-CINAHL and Web of Science was performed. The following search terms were used on the Medline-OVID database: "type 2 diabetes mellitus AND exercise (focus)," AND "metformin OR rosiglitazone." The following search terms were used on the EBSCO-CINAHL database: "diabetes," AND "exercise," AND "insulin sensitivity," AND "metformin OR rosiglitazone." The following search terms were used on Web of Science: "insulin sensitivity," AND "exercise," AND "diabetes mellitus type 2" AND "metformin OR rosiglitazone."

Inclusion criteria for articles included in the systematic review included those using metformin or rosiglitazone or a combination of the two drugs with a concurrent exercise regimen and measuring glycemic indices. Articles were excluded if they were
not published in English, if exercise was only used at the beginning and end of the study, if it focused on medications other than metformin or rosiglitazone and if they did not measure insulin sensitivity or fasting glucose levels.

Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). 8

RESULTS

The Medline-OVID search resulted in a total of 25 articles, while the EBSCO-CINAHL search resulted in a total of 15 articles and the Web of Science search resulted in a total of 48 articles. Once articles were screened for inclusion criteria, exclusion criteria, and duplicates were accounted for, two articles were deemed of high relevance for this systematic review. The two studies included in the systematic review are detailed in Table I.

Independent and Combined Effects of Exercise Training and Metformin

In 2011, Malin et al 9 from the University of Massachusetts, Amherst, conducted a study to determine the independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. The study participants were 32 individuals with impaired glucose tolerance who were recruited from the local community via flyers and newspaper advertisements. The article does not mention any randomization of treatment. Participants were assigned to one of four interventions: placebo, metformin, exercise training with placebo, or exercise training with metformin. Participants included 12 males and 20 females between the ages of 35 and 65, and included both pre and postmenopausal women. Participants were enrolled in the study if they were nonsmoking, weight stable, free of cardiovascular disease or diabetes, had any
contraindications to metformin, and were not taking dietary supplements or medications that would affect insulin sensitivity. As a result of the community that they were recruited from, the racial makeup of the participants included 27 Caucasians, three African Americans, and two Hispanics. The study lasted a total of 12 weeks.9

A double-blind design was used to distribute pills and subjects taking the pills were told to do so with food to minimize potential side effects. Initially subjects were treated with 500 mg/day of metformin and the dose was increased by 500 mg/day each week until reaching a clinical dose of 2000 mg/day by week four. The clinical dose was taken for the remaining eight weeks of the 12-week study. Exercise was supervised three days a week for 60-75 minutes per session. Aerobic and resistance exercise was performed on the first and third day of each week, while only aerobic exercise was performed on the second day of exercise each week to minimize muscle soreness. The first five minutes was a warm up on a cycle ergometer, followed by 45 minutes of cycling at 70% baseline peak heart rate. Resistance exercise was performed at 70% the subjects baseline one repetition maximum. Once a participant could lift two sets of 12 repetitions with proper form, weight was increased by about five percent. All major muscle groups used during chest press, latissimus pull-down, leg press, bicep curl, triceps push-down and upright row exercises were targeted by the resistance training.9

Measurements of insulin, glucose, C peptide, nonesterified fatty acids and stable isotope enrichment were performed at the beginning and end of the study using a euglycemic hyperinsulinemic clamp. Each of the interventions resulted in 13-25% lower fasting insulin concentrations (P < 0.05) yet there was no difference among the...
interventions. Both hepatic glucose production and insulin sensitivity were unaffected after any treatment.\textsuperscript{9}

**Exercise Training Ameliorates the Effects of Rosiglitazone**

In 2009, Kadoglou et al\textsuperscript{10} conducted a study to determine how exercise training interacts with rosiglitazone to improve cardiovascular risk factors in patients with T2DM. The study participants were 100 white patients with T2DM, between the ages of 50 and 70 years, and were recruited from an outpatient diabetic clinic. The patients eligible for the study had been receiving metformin and gliclazide treatment for at least six months without adequate glycemic control. Patients were ineligible if they had diabetic vascular complications, chronic heart failure, liver or renal impairment, uncontrolled hypertension, arrhythmias, orthopedic problems or life threatening diseases. They were also excluded if they were on lipid lowering medication, hormone replacement therapy, insulin, thiazolidinedione treatment or were active smokers. The study lasted 12 months and the patients were randomly assigned to the following age and sex matched groups: control group, addition of rosiglitazone, adjunctive exercise program, and addition of rosiglitazone and adjunctive exercise program. The control group maintained their current habitual activities while groups receiving rosiglitazone received 8 mg/day.

Patients were assigned through a computer generated random list on a database protected by a password.\textsuperscript{10}

Patients that were assigned to receive exercise treatment attended the same fitness center four times a week to perform aerobic exercise. The intensity of the exercise sessions was individuated by an initial ergocycle test. Each session was 45-60 minutes long including a 10 minute warm up and five minute cool down. During the course of the
first month the workload was increased until subjects achieved 50% to 80% peak oxygen consumption for 45 minutes. Exercise included walking or running on a treadmill, cycling and calisthenics involving large muscle groups. Exercise remained constant until the eighth month, when subjects could continue the exercise in a self-controlled lifestyle program including brisk walking, jogging and daily activities for more than 150 minutes per week. Patients kept their own personal diary of activity records that were checked every two weeks for compliance. This study showed that despite going from a structured exercise program to a self-controlled exercise program, the exercise treated patients were able to maintain the exercise related benefits from the initial eight months and have persistent benefits in glycemic control.  

Blood samples were obtained at baseline and at the end of the study. These blood samples looked at glucose, hemoglobin A1c (HbA1c) and insulin levels among many other outcomes. HbA1c levels changed most drastically in the rosiglitazone and exercise group with a -1.52% +/- 0.91% from baseline. Exercise alone resulted in a HbA1c -0.29% +/- 0.57% from baseline while rosiglitazone alone was -0.83% +/- 0.89% from baseline. The rosiglitazone with exercise group had the most improved glycemic control, accounting for 76.7% of the patients in the study who reached the glycemic target of having a HbA1c below seven percent at the end of the study. 

**DISCUSSION**

The findings from these studies should be considered when dealing with patients with or at risk of developing T2DM. Metformin is shown to limit exercise capacity while rosiglitazone is shown to actually improve exercise capacity in those with T2DM. Over time, these effects may interact so that metformin and exercise do not have additive
affects on glycemic control while rosiglitazone plus exercise does. This knowledge is important when deciding how to individualize treatment for a patient with T2DM. If a patient is motivated to begin a supervised exercise program, it may be more beneficial to prescribe rosiglitazone instead of metformin. If this patient were to receive metformin, it has the potential to increase resting heart rate and decrease peak heart rate, limiting their ability to exercise. This patient may become less motivated to exercise, and even if they were to exercise, the affects of the two treatment modalities together may not be additive. This same patient on rosiglitazone will have improvements in exercise capacity, which may result in a more motivated patient. The combined treatment modalities of exercise and rosiglitazone will also have additive affects on glycemic control by increasing exercise capacity and motivation, improving insulin secretion and sensitivity, decreasing HbA1c and lowering fasting glucose levels.

**Independent and Combined Effects of Exercise Training and Metformin**

This study found that the addition of metformin to exercise training does not accentuate the effects on the whole body insulin sensitivity of exercise alone. 9

The quality of evidence from this study is very low. This study has a small sample size with only 32 participants. It also does not mention any form of randomization when allocating group assignments. The small study size that is characteristic of that community, which is mainly Caucasian, is not characteristic of all communities. This study also does not look at an equal number of men and women or the younger population, which has a rapidly growing risk of developing T2DM. The study period of 12 weeks is too short to see how much the treatment modalities interact. 9
The article states that no potential conflicts of interest were reported relevant to this article. However, there are many areas in which bias may have affected this study. Selection bias may have occurred because subjects of the study were recruited via flyers and newspaper advertisements. There is no mention of these flyers or advertisements in languages other than English. Furthermore, there was no mention of randomization in the study. Blinding occurred during pill distribution to patients, but it impossible to blind them to the fact that they are either doing an exercise regimen or not.

Exercise Training Ameliorates the Effects of Rosiglitazone

This study found that the group with greatest benefit on glycemic control was exercise training in addition to rosiglitazone compared to either treatment alone.

The quality of evidence from this study is low. Participants of the study were randomized and there were a total of 89 people analyzed after loss to follow up. The study lasted 12 months, which allowed for the treatments to interact for a longer period of time.

There are limitations to this study. All of the study participants in this study were Caucasian and belonged to an older age group. This limits the study results to a fairly specific population group. Also, to measure insulin sensitivity they used a homeostasis model assessment (HOMA-IR) that reflects both peripheral and hepatic insulin sensitivity. Furthermore, the last four months of the exercise regimen was self reported and leaves room for reporting bias from the patients. Also, insulin sensitivity measurements were not taken at the eight month mark so there is no way to determine how the period of self controlled exercise affected the glycemic controls over the last four months of the study.
CONCLUSION

There are many studies exhibiting the interactions between metformin and
rosiglitazone and the ability of patients to exercise but there are few studies analyzing the
interactions between exercise and diabetic medications over time and their affects on
diabetic disease markers such as insulin sensitivity and HbA$_1$c. These studies show that
rosiglitazone has additive effects with exercise while metformin does not. The evidence
on the subject of this review is lacking and the quality of the evidence is not sufficient to
make strong conclusions.

Future research is needed to confirm and expand on the results of the studies in
this review. The studies should be over a longer period of time, with a greater number of
study participants to determine how large of an effect the interaction between treatment
modalities is. Studies should focus on both younger populations and older ones.
Randomization of participants needs to have a greater focus, along with blinding and
concealment when possible. HbA$_1$c and fasting glucose levels should be outcomes that
are measured since those are the measurements used to determine the diagnosis of
T2DM.
References


Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Total subjects at the beginning of study</th>
<th>Total subjects analyzed at end of study</th>
<th>Follow up period</th>
<th>Description of loss to follow-up</th>
<th>Intervention Groups</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding of outcome assessors</th>
<th>Quality of Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malin et al(^9)</td>
<td>32</td>
<td>Unclear</td>
<td>12 weeks</td>
<td>Unclear</td>
<td>Control, Metformin, exercise with placebo, exercise with metformin</td>
<td>Unclear</td>
<td>Adequate</td>
<td>Unclear</td>
<td>Very Low*</td>
</tr>
<tr>
<td>Kadoglou et al(^10)</td>
<td>100</td>
<td>89</td>
<td>12 months</td>
<td>Yes</td>
<td>Control, add on rosiglitazone, adjunctive exercise program, add on rosiglitazone and adjunctive exercise program</td>
<td>Adequate</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low#</td>
</tr>
</tbody>
</table>

\(^*\)Quality is very low due to unclear randomization and loss to follow up, small study size and short study duration

\(^\#\)Quality is low because it only looked at white patients, concealment was unclear and there was no data collection between changing exercise regimens